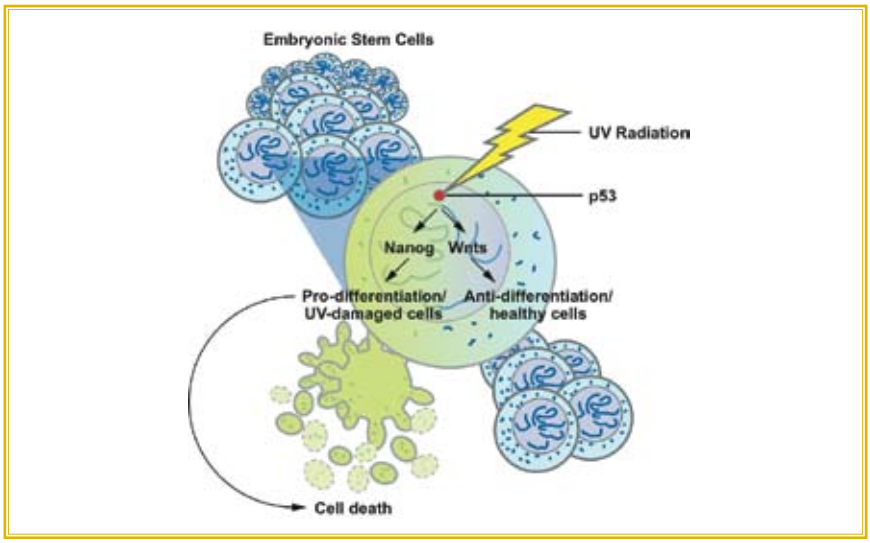
The Dual Effects of p53 on Differentiation

The p53 protein promotes differentiation and activates Wnt-mediated anti-differentiation in mouse embryonic stem cells.



(*Image: J. Kelly*)

The transcription factor protein p53 in UV-damaged embryonic stem cells both promotes differentiation and activates Wnt-mediated anti-differentiation.

DNA damage can have serious consequences in any cell. When it occurs in embryonic stem cells, however, the consequences can be even more devastating since the resulting mutations will be passed on in all subsequent cell divisions. It is therefore critical for a cell to have several sensor mechanisms in place to detect and hopefully repair such damage. One such sensor is p53, a transcription factor protein and so-called tumor suppressor that monitors cells for damage from many types of environmental stress. When damage occurs, p53 activates specific pathways to assess the damage and prevent its spread by inhibiting cell division or causing the cell to undergo programmed cell death.

Although the functions of p53 have been extensively researched in adult cells, they are largely unknown in embryonic stem cells. Jing Huang, Ph.D., Head of the Cancer and Stem Cell Epigenetics Section at CCR, along with Postdoctoral Fellow Kyoung-Hwa Lee, Ph.D., and their colleagues recently published a report in the December 14, 2009 issue of *Proceedings of the National Academy of Sciences* that identifies a mechanism used by p53 to control the fate of mouse embryonic stem cells upon DNA damage.

To determine the genes affected by p53 in mouse embryonic stem cells, the scientists identified the p53 binding sites on cellular DNA using a genome-wide approach called chromatin immunoprecipitation-based microarray (ChIP-chip). They compared the binding of p53 in normal cells and in cells with DNA damage from adriamycin, an anti-cancer drug, and found that, when DNA damage occurred in embryonic stem cells, p53 strongly enhanced the expression of genes associated with the Wnt signaling pathway. The researchers measured the ability of p53 to activate Wnt signaling in cultured mouse embryonic stem cells and found that the cells secreted specific Wnt proteins into the culture media that inhibit differentiation of surrounding cells. If the cells were modified to remove p53, Wnt production was diminished.

The direct connection of p53 to Wnt-mediated suppression of cell differentiation was puzzling at first since p53 is known to promote differentiation as a means of removing unhealthy cells from the stem cell pool. But the researchers concluded that p53 is essentially using its ability to both promote and inhibit the differentiation of embryonic stem cells to perform its role as a stress sensor, monitoring its cellular environment and reacting accordingly. When damage occurs, p53 does indeed remove unhealthy cells from the stem cell pool by promoting programmed cell death or differentiation. At the same time, p53 activates the Wnt pathway to inhibit the differentiation of surrounding, healthy embryonic stem cells to maintain a population for the development of the organism.

The next step is to determine whether mutations in p53 may restore its control of Wnt signaling, not only in embryonic stem cells but also in adult cells. Overactivation of Wnt is tumorigenic in certain somatic cells, so p53-activated Wnt signaling could become oncogenic. "If we can understand how p53 can be converted from a tumor suppressor to an oncogene," said Dr. Huang, "perhaps we can target the p53 mutant to fight cancer."

To learn more about Dr. Huang's research, please visit his CCR Web site at ***http://ccr.cancer.gov/staff/staff.asp?Name=jinghuang****.*